CRITICAL CARE

REVIEW

# Bench to bedside review: Extracorporeal carbon dioxide removal, past present and future

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**Abstract**

Acute respiratory distress syndrome (ARDS) has a substantial mortality rate and annually affects more than 140,000 people in the USA alone. Standard management includes lung protective ventilation but this impairs carbon dioxide clearance and may lead to right heart dysfunction or increased intracranial pressure. Extracorporeal carbon dioxide removal has the potential to optimize lung protective ventilation by uncoupling oxygenation and carbon dioxide clearance. The aim of this article is to review the carbon dioxide removal strategies that are likely to be widely available in the near future. Relevant published literature was identified using PubMed and Medline searches. Queries were performed by using the search terms ECCOR, AVCO2R, VVCO2R, respiratory dialysis, and by combining carbon dioxide removal and ARDS. The only search limitation imposed was English language. Additional articles were identified from reference lists in the studies that were reviewed. Several novel strategies to achieve carbon dioxide removal were identified, some of which are already commercially available whereas others are in advanced stages of development.

## Introduction

The reported incidence of acute respiratory distress syndrome (ARDS) ranges from 7 to 59 per 100,000 people [1,2], and is associated with a mortality rate of 40 to 45%. This rate remains unacceptably high despite the introduction of lung protective ventilation and, although hospital mortality may be slowly decreasing, ICU and 28 day mortality have remained constant [1,3]. Failure to implement lung protective ventilation (LPV) may be one of the reasons ICU mortality rates have remained unchanged [4-6]. When surveyed, health care providers reported that hypercapnia or its related effects were significant barriers to achieving LPV [7]. Hypercapnia complicated 14% of patients in the large ARDS network on the use of LPV [8]. However, patients with a high risk of death were excluded. In a study of severe ARDS, where tidal volumes were adjusted to target a mean airway pressure less than 28 $cmH_2O$, all patients experienced hypercapnia [9]. As evidence emerges that tidal volumes <6 $ml.kg^{-1}$ might further reduce mortality [9,10], alternative strategies to manage the inevitable hypercapnia must be considered.

Permissive hypercapnia is one approach, but it only improves mortality when patients are ventilated with high tidal volumes [8]. Such volumes should no longer be used since 6 $ml.kg^{-1}$ is superior to 12 $ml.kg^{-1}$ and <4 $ml.kg^{-1}$ might be superior to 6 $ml.kg^{-1}$ [9-11]. Although hypercapnia might have beneficial effects on oxygen delivery and attenuation of inflammation [12], it also harms injured lung through immunosuppression and impaired pulmonary epithelial repair [13,14]. Furthermore, hypercapnia perpetuates right heart failure [15] and is undesirable in patients with elevated intracranial pressure. An alternative strategy to manage hypercapnia is extracorporeal carbon dioxide removal (ECCOR), a technology pioneered four decades ago [16] but only recently readily accessible through commercialization of several novel devices. ECCOR therefore deserves a fresh look and this review aims to provide an overview of devices currently available and those that may be available in the near future.

## ECCOR in principle

ECCOR is designed to remove carbon dioxide ($CO_2$) and, unlike extracorporeal membrane oxygen (ECMO), does not provide significant oxygenation. A discussion of ECMO is beyond the scope of this article but is well reviewed elsewhere [17,18]. In its simplest form, ECCOR consists of a drainage cannula placed in a large central vein, a pump, a membrane lung and a return cannula (Figure 1). Blood is pumped through the membrane

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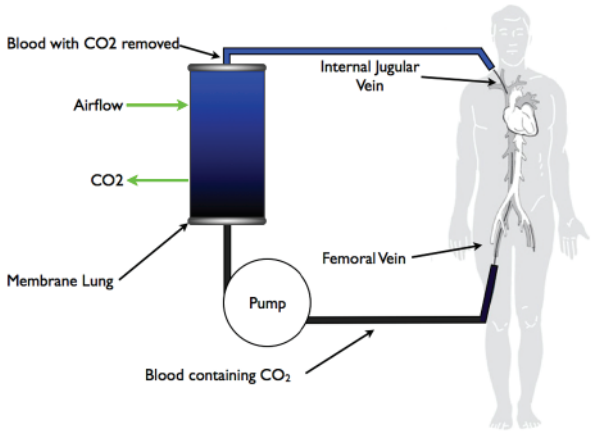


**Figure 1. Diagram demonstrating essential components of an extracorporeal carbon dioxide removal circuit.**

'lung' and $CO_2$ is removed by diffusion. Membrane lungs are permeable to gases but not liquids. A flow of gas containing little or no $CO_2$ runs along the other side of the membrane, ensuring the diffusion gradient favors $CO_2$ removal.

In contrast to ECMO, where the need for oxygenation requires high blood flow rates, ECCOR allows much lower blood flow rates, a result of major differences in $CO_2$ and oxygen ($O_2$) kinetics. First, almost all the $O_2$ in blood is carried by hemoglobin, which displays sigmoidal saturation kinetics. Assuming normal hemoglobin and venous $O_2$, each liter of venous blood can only carry an extra 40 to 60 ml of $O_2$ before the hemoglobin is saturated. Blood flows of 5 to 7 L.minute$^{-1}$ are therefore required to supply enough $O_2$ for an average adult (250 ml. minute$^{-1}$). Conversely, most $CO_2$ is transported as dissolved bicarbonate, displaying linear kinetics without saturation. Thus, 1 L of blood is capable of carrying more $CO_2$ than $O_2$, and 250 ml of $CO_2$ can be removed from <1 L of blood. Second, $CO_2$ diffuses more readily than $O_2$ across extracorporeal membranes because of greater solubility [17].

### The membrane lung

The membrane lung made long-term extracorporeal gas exchange feasible. Before membrane lungs, extracorporeal circuits achieved gas exchange by creating a direct air-blood interface, either bubbling air through blood or creating a thin film of blood on the surface of a rotating cylinder/disc. However, blood-air interfaces denature proteins, activate clotting and inflammatory pathways, and damage circulating cells [19]. Consequently, devices relying on blood-air interfaces cannot be used more than a few hours without serious complications.

The concept of placing a barrier between blood and air began with the observation that gas exchange occurred across cellophane tubing in hemodialysis machines [20]. This led to the development of membrane lungs consisting of gas permeable silicone-rubber mounted on a nylon mesh [21]. The nylon mesh provided structural strength and decreased leakage from random pinhole defects, which occur during the manufacture of thin silicone-rubber membranes [19]. Three major factors determine the amount of gas crossing membranes: the diffusion gradient, the membrane-blood contact time and the membrane diffusion characteristics.

The $CO_2$ diffusion gradient is determined by the $CO_2$ content of the blood and the air passing through the membrane lung, as well as the speed of the airflow. Membrane-blood contact time is determined by membrane geometry. In early devices, Theodore Kolobow arranged the membrane into a coil [22] and used a fabric with an irregular surface, increasing the surface area [23]. Hollow fiber membranes have now replaced coiled silicon-rubber membranes. Early fibers were constructed with microporous polypropylene. Micropores create microscopic blood-gas interfaces allowing efficient gas exchange, but also cause plasma leak. Recently, non-microporous poly-4-methyl-1-pentene (PMP) has been used; it provides superior gas exchange, better biocompatibility and is less susceptible to plasma leak [24-26]. Adding covalently bound heparin to membrane surfaces enhances biocompatibility, and gas exchange has been improved by arranging fibers into a complex mat and running blood on the outside [27] (Figure 2). This arrangement allows perpendicular blood flow to the fibers, improving mass transfer by reducing the diffusion path length compared to parallel flow. Modern membrane lungs achieve adequate gas exchange with surface areas of 1 to 3 m$^2$ (Table 1).

### The pump

Blood flow through ECCOR circuits can be achieved in one of two ways. In patients with sufficient arterial pressure, a pumpless system can be used where blood is driven out of an arterial cannula by high arterial pressures and returned through a venous cannula, often called arteriovenous $CO_2$ removal (AVCO2R). Pumpless systems result in less blood trauma, but require large bore arterial cannulas and an adequate cardiac output. The alternative is to use a mechanical pump.

Early devices used roller or peristaltic pumps. Although cheap and reliable, these pumps were prone to blood trauma - for example, hemolysis - from compression and heating of blood components. Blood trauma is less of a problem at lower blood flow rates - for example, those used in dialysis. The introduction of rotary pumps has resulted in simpler yet effective systems that cause less blood trauma. Two main types of rotary pumps are used in ECCOR devices, centrifugal and diagonal flow pumps.

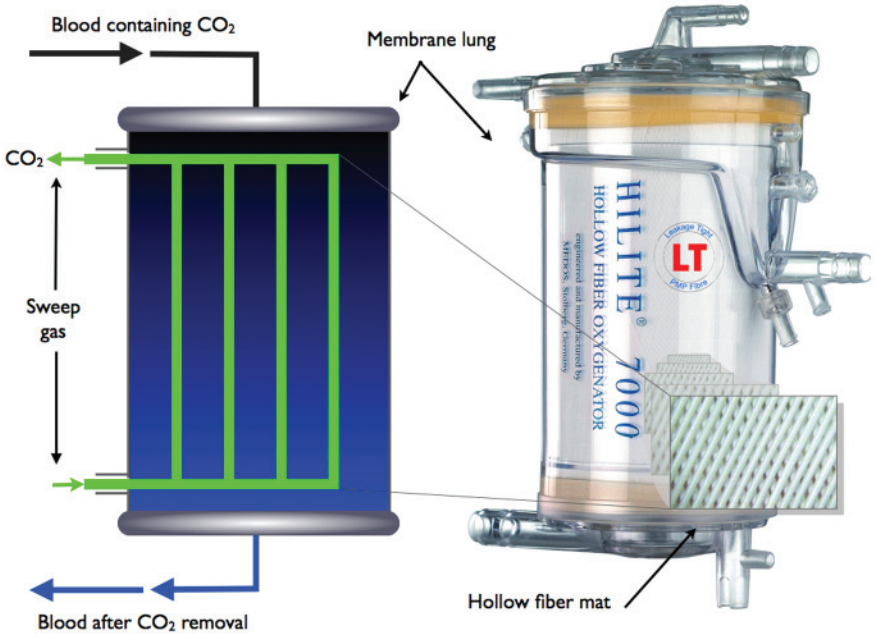


**Figure 2. Diagram showing the basic principle of a membrane lung.** Sweep gas passes through the hollow fibres. Hollow fibers are arranged in a complex mat. Image courtesy of Medos Medizintechnik AG (Stolberg, Germany).

Centrifugal pumps use a radial rotating impeller to create a suction vortex that draws blood into the center of the pump and spins it outwards, imparting centrifugal momentum, which is converted into driving pressure. In diagonal flow pumps, impellor design is a mix of radial and axial geometry. Centrifugal pumps tend to generate high pressures and low flows, whereas diagonal pumps produce both high flows and high pressures [28]. Impellors are connected to a drive shaft, requiring bearings to support the rotational movement. Exposure of blood to typical bearings promotes clotting, causing deposition of coagulation debris that can seize the bearing. Some pumps use seals to protect the bearings, but these can wear out; other designs use biocompatible materials to construct the bearings. In the most advanced centrifugal pumps impellors are completely suspended in an electromagnetic field, eliminating the need for a drive shaft or bearings and reducing heating, minimizing blood trauma and lowering the incidence of mechanical failure.

### Access cannula

Early clinical trials placed separate drainage and return cannulas in the saphenous veins [29,30]. Modern cannulas are placed percutaneously in a femoral-femoral or femoral-jugular orientation. To maintain flow and minimize blood trauma, heparin-coated wire-reinforced cannulas are used. Recently, a high flow, wire-reinforced double-lumen catheter has been developed. It is placed via the right internal jugular vein and the drainage port (tip of the cannula) is advanced into the intra-hepatic inferior vena cava using ultrasound guidance [31]. In this orientation the return port aligns with the right atrium, minimizing recirculation. New ECCOR devices with flow rates comparable to those in dialysis use double-lumen cannulas similar to dialysis catheters [32,33].

## ECCOR in practice

The first clinical trial of extracorporeal respiratory support was published in 1979, and used the Kolobow spiral-coil membrane lung, a roller pump and veno-arterial access to provide ECMO [34]. This trial found no difference between conventional treatment and ECMO. At about the same time Gattinoni and coworkers introduced ECCOR [35], but did not publish the first clinical trial until 1986, where patients with severe ARDS were selected for LPV combined with ECCOR (Kolobow spiral-coil membrane lung, and a roller pump). Observed mortality was 51% using this technique [29]. Subsequent work was initially encouraging [36] but a randomized controlled study in 1994 concluded that ECCOR conferred no survival advantage [30]. Importantly, complication rates were high with ECCOR, being discontinued in 33% of cases owing to bleeding, and 20% experiencing circuit clotting. Recently, new devices with lower complication rates have demonstrated improved survival when combined with ultra-protective ventilation [9]; some are already available whilst others are in advanced development. They can be broadly categorized into i) arteriovenous devices, ii) venovenous devices, iii) gas exchange catheters and iv) respiratory dialysis.

**Table 1. Extracorporeal carbon dioxide removal circuit components**

| Component | Name | Special features | Manufacturer |
|---|---|---|---|
| Pump | Centrimag | Impeller elevated in electromagnetic field | Levotronix LLC Waltham, MA, USA |
| | RotaFlow | Impeller driven by electromagnetic field and has single sapphire bearing | Maquet, Rastatt, Germany |
| | Biomedicus | Impeller drive shaft supported by sealed bearings | Medtronic, Eden Praire, MN, USA |
| | Deltastream | Diagonally streamed impeller, sealed bearings | Medos Medizintechnik AG, Stolberg, Germany |
| Membrane lung | Quadrox D | 1.8 $m^2$ surface area, 250 ml priming volume | Maquet, Rastatt, Germany |
| | iLA membrane ventilator | 1.3 $m^2$ surface area, 175 ml priming volume | Novalung GmbH, Heilbronn, Germany |
| | hilite 7000LT | 1.9 $m^3$ surface area, 275 ml priming volume | Medos Medizintechnik AG, Stolberg, Germany |
| | Affinity NT | 2.5 $m^2$ surface area, 270 ml priming volume | Medtronic, Eden Praire, MN, USA |

This list is not exhaustive, but demonstrates the range of products available. iLA, interventional lung assist.

## Arteriovenous carbon dioxide removal

AVCO2R is commercially available through Novalung (GmbH, Hechingen, Germany) and marketed as the interventional lung assist (iLA) membrane ventilator (Figure 3). The membrane lung, frequently called the 'Novalung,' utilizes a low resistance design allowing blood flow using the patient's own arteriovenous pressure gradient. Cannulas are placed percutaneously in the femoral artery and vein [37,38]. A similar system has been developed in the United States using the Affinity NT (Medtronic, Minneapolis, MN) [39,40].

Pumpless systems require an arteriovenous pressure gradient ≥60 mmHg, which is unsuitable for hemodynamically unstable patients. Further, cannulation of a major artery can result in distal ischemia [37], although measuring the artery diameter with ultrasound and selecting a cannula that occupies no more than 70% of the lumen reduces this risk [38]. AVCO2R has been successfully used to facilitate LPV in patients with ARDS [41-43], severe asthma [44] and as a bridge to lung transplantation [45].

## Venovenous carbon dioxide removal

Venovenous carbon dioxide removal (VVCO2R) requires a mechanical pump to propel blood through the circuit and can be broadly divided depending on whether the pump and membrane lung are separate components or incorporated into a single console. When separate components are used, the circuit is set up as described in Figure 1. Table 1 shows some of the different components that can be used. These circuits are more complicated to operate, often need flow rates >1 $L.minute^{-1}$ and may need multidisciplinary support. The growth of programs in more general settings has provided impetus to simplify ECCOR, resulting in several devices where the pump and membrane lung are combined into one console.

### iLA Activve

The iLA Activve mounts the Novalung and a diagonal flow pump together in one device. At higher blood flow rates this device can provide venovenous ECMO. Conceptually, this is the simplest method of providing ECCOR via a console, and although it does not provide any special benefits over separate components, the pump is designed to provide reliable flows throughout a large range of flow rates.

### Decap/Decapsmart

The Decap system (Hemodec, Salerno, Italy) uses a membrane lung in series with a hemodialysis filter and roller pump (Figure 4). The hemodialysis filter serves two purposes with regard to $CO_2$ removal. First, it reduces the chance of bubble formation by increasing resistance within the membrane lung. Second, ultrafiltrate from the filter is returned to the blood stream prior to the membrane lung inflow. Since ultrafiltrate contains dissolved $CO_2$, recirculating in this way allows additional $CO_2$ removal by creating a greater flow rate through the membrane lung than the flow from the patient. Consequently, smaller membrane lungs can be used (0.3 to 1.35 $m^2$) with lower flow rates (<500 $ml.minute^{-1}$) than conventional ECCOR [33], resulting in similar anticoagulation requirements to continuous venovenous hemodialysis [46]. The Decap has been successfully used in adults and children [9,47,48].

### Hemolung

The Hemolung (Alung Technologies, Pittsburgh, USA) is the latest device to enter the ECCOR arena. In this device the membrane lung and centrifugal pump are combined together, acting as one unit (Figure 5). Blood is drawn into the unit via a rotating impeller. The center contains a rotating core that accelerates blood towards a surrounding stationary fiber bundle. This is called active mixing; the rotating core generates disturbed blood flow patterns subjacent to the fiber membrane, reducing diffusional resistance and increasing gas exchange. As a result, $CO_2$ removal is more efficient and achieved with a smaller membrane surface area and flows of 400 to 600 $ml.minute^{-1}$,

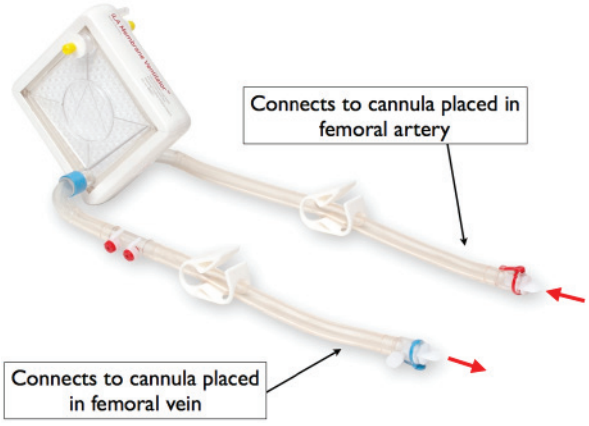


**Figure 3. Image of the interventional lung assist (iLA), blood is propelled through the circuit by arterial pressure.** Image courtesy of Novolung (GmbH, Hechingen, Germany).

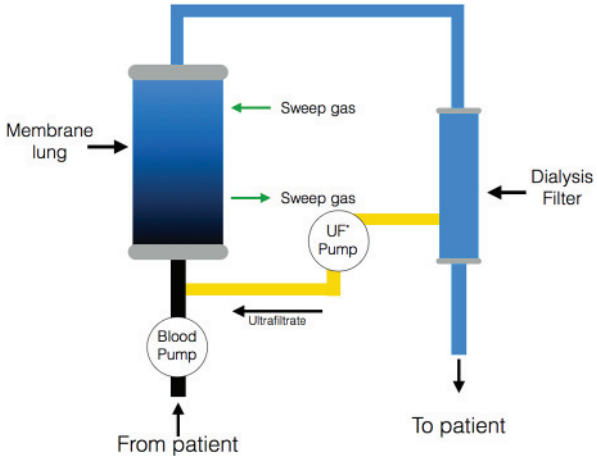


**Figure 4. Diagram showing the basic circuit design of the Decap (Hemodec, Salerno, Italy).** Blood is pumped through a membrane lung in series with a dialysis filter, and ultrafiltrate is returned to the blood prior to the membrane. UF, ultrafiltrate.

which allows use of smaller double-lumen catheters. The smaller membrane surface area, siloxane coating for plasma resistance and covalently bound heparin result in lower anticoagulation requirements [32]. Gas flow through the membrane lung is supplied under negative pressure, a safety feature preventing air embolism if the membrane is disrupted. The Hemolung enabled a 50% reduction in minute ventilation in animal trials and was recently successfully used in a clinical case series of five adults [49].

## Gas-exchange catheters

Several gas-exchange catheters have been developed but only one, the intravenocaval oxygenator and carbon dioxide removal device (IVOX), has been used clinically. These devices package hollow fiber membrane lungs into a catheter that is small enough to be placed in the vena cava, that is, <15 mm in diameter. Intracorporeal catheters are conceptually attractive because they are exposed to 2 to 3 L.minute$^{-1}$ of blood flow and therefore $CO_2$ removal is not flow limited.

The IVOX was designed for both oxygenation and $CO_2$ removal. Orienting 'crimped' membrane fibers in a spiral arrangement maximized gas exchange by increasing surface area and creating disturbed blood flow patterns over the membrane [50]. Disturbed blood flow provides convection velocity towards the fiber surfaces, reducing diffusional resistance. The membrane surface of the IVOX ranged from 0.2 to 0.5 m$^2$ [51] and gas flow was applied under negative pressure; an important safety feature in intracorporeal devices since there is no other opportunity to prevent air embolism if the membrane is disrupted.

In animal trials the IVOX consistently removed 40 ml.minute$^{-1}$ of $CO_2$, but oxygen delivery was less reliable. Clinical experience was mixed; the IVOX facilitated lower ventilator settings in some studies [52], but made no difference in others [53,54]. On the whole, gas exchange was too limited and placement associated with high complication rates from bleeding and thrombosis [52]. Commercial development has subsequently ceased.

## Future directions and devices in development

Several of the above devices are undergoing clinical trials, often in combination with LPV (Table 2). Other promising approaches are still in development, in particular more efficient gas exchange catheters and respiratory dialysis. Novel methods to maximize $CO_2$ removal, such as blood acidification, are also under investigation [55].

### Gas-exchange catheters in development

Following the IVOX, attention has focused on developing a catheter that meets 50% of adult gas exchange requirement. Several ingenious approaches are being studied. The first approach is generation of active mixing within the catheter. This was initially attempted using an intra-aortic balloon pump close to the shaft of the IVOX catheter [56]. However, the membrane fibers were not fixed and fiber movement opposed active mixing. The Hattler catheter solved this using a rigid fiber mat constructed around a central balloon [57] (Figure 6). Rapid pulsation of the balloon directed blood flow over the membrane fibers, causing active mixing. In this design membrane fibers do not occupy the whole lumen of the vein, causing less fiber drag on blood flow. In animal trials the Hattler catheter exchanged $CO_2$ at 305 ml.minute$^{-1}$.m$^{-2}$, almost double the IVOX rate at similar $CO_2$ concentrations [58,59].

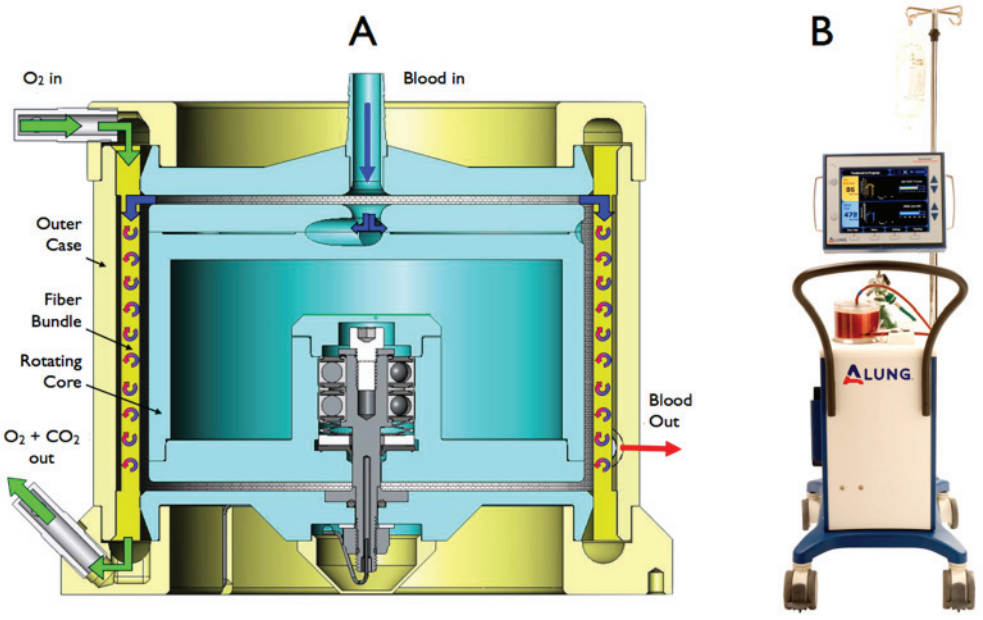


**Figure 5. Cross sectional diagram of Hemolung (Alung Technologies, Pittsburgh, USA) showing rotating core that accelerate blood to the surrounding fiber bundle.** Adjacent image shows the Hemolung console. Courtesy of Alung Technologies (Pittsburgh, USA).

**Table 2. Current active trials from clinicaltrials.gov accessed April 2012**

| Study title | Device | Sponsor | Status |
|---|---|---|---|
| Extracorporeal $CO_2$ removal in COPD (DECOPD) | Decap Smart | University of Turin, Italy | Recruiting |
| Pulmonary and Renal Support during Acute Respiratory Distress Syndrome (PARSA) | Neonatal membrane lung (HiLite 800 LT, Medos) within dialysis circuit (Multifiltrate kit 7, CVVH 1000, Fresenius) | Hopital Ambroise Pare, France | Recruiting |
| Low-flow ECCO2-R and 4 ml/kg Tidal Volume vs. 6 ml/kg Tidal Volume to Enhance Protection From Ventilator Induced Lung Injury in Acute Lung Injury (ELP) | Not specified | University of Turin, Italy | Not yet recruiting |

Active mixing can also be achieved by rotating the fiber bundle; a strategy used in the dynamic intravascular lung assist device (D-ILAD) [60]. Although the D-ILAD was almost twice as efficient as balloon-pulsating catheters, rotating fibers could damage vessel walls upon contact. Recently, the Hattler catheter has been modified by replacing the balloon with a series of small impellers. It has been successfully used in animals and has $CO_2$ exchange rates similar to the D-ILAD [61].

Finally, in addition to active mixing, $CO_2$ exchange has been improved by covalent immobilization of carbonic anhydrase to the surface of the hollow fiber membrane [62]. As a result, $CO_2$ is more rapidly generated from bicarbonate, facilitating removal.

### Respiratory dialysis

In the 1980s, several groups reported the results of animal experiments using dialysis to remove $CO_2$ in the form of bicarbonate. This approach is appealing because $CO_2$ is transported in the form of bicarbonate, which moves freely across dialysis membranes. Conventional hemodialysis uses bicarbonate-containing dialysates to correct the metabolic acidosis accompanying renal failure, but bicarbonate-free dialysates can remove enough $CO_2$ to replace pulmonary ventilation in dog models [63]. Currently, respiratory dialysis is limited by the inability to maintain electrolyte concentrations and pH whilst removing bicarbonate. Several approaches to replace bicarbonate have been attempted using sodium hydroxide, tromethamine (THAM), and organic anions. However, fluid gain, hyperchloremic acidosis, hemolysis, cardiac arrhythmias and acid-base derangements have prevented successful long-term use [64,65].

Recently, hemofiltration has been used to remove bicarbonate. One group used sodium hydroxide in a post-filter replacement fluid and maintained pH and $CO_2$

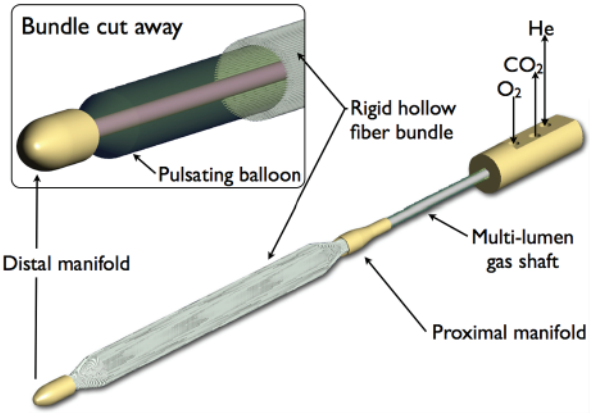


**Figure 6. Diagram of the Hattler catheter showing the rigid hollow fiber bundle surrounding a pulsating ballon.**

within physiological range for 18 hours in hypoventilated sheep. However, hyperchloremic acidosis developed and blood flow rates exceeding 500 ml.minute$^{-1}$ would be needed to remove sufficient $CO_2$ in humans [66]. Another group removed bicarbonate by using pre-filter replacement fluid containing THAM. Physiologic $CO_2$ levels and pH were maintained for 1.5 hours, but it was not determined whether THAM had the same long-term problems seen in the hemodialysis models [67]. Nonetheless, respiratory dialysis holds much promise if the problems of electrolyte and acid-base disturbances can be solved.

## Conclusion

Several modalities of providing ECCOR are now either available or in development. As evidence favoring low-volume, low-pressure ventilation in ARDS accumulates, the argument for applying these ventilation strategies in all critically ill patients will gather momentum. However, successful application is dependent upon a safe, reliable approach for $CO_2$ removal.

Simpler more efficient ECCOR devices requiring lower blood flow rates and smaller access cannulas promise to improve safety and ease of use. Novel designs, such as the Decap, can serve the dual purpose of renal support and ECCOR. However, other solutions currently in development, gas exchange catheters and respiratory dialysis, promise to be minimally invasive, easy to initiate and well tolerated. They may even eliminate the need for intubation in some forms of respiratory failure, where $CO_2$ is the primary problem [68]. Familiarity with devices already available can change our approach to ARDS and prime the ICU for the arrival of devices that may revolutionize our approach to respiratory failure.

### Abbreviations

ARDS, acute respiratory distress syndrome; AVCO2R, arteriovenous $CO_2$ removal; D-ILAD, dynamic intravascular lung assist device; ECCOR, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygen; iLA, interventional lung assist; LPV, lung protective ventilation; THAM, tromethamine; VVCO2R, venovenous carbon dioxide removal.

### Competing Interests

MEC and GM have no competing interests to declare. WJF is head of the scientific advisory board at ALung Technologies, and has an equity interest in this company. JAK is a paid consultant for ALung Technologies.

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